

# LYON WORKSHOP ON CLINICAL RESEARCH AND HEALTHCARE OUTCOMES

## Draft Summary Report

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Clinical trials and studies are essential to the progress of evidence-based medicine. Randomised clinical trials provide the highest levels of evidence, and this evidence allows healthcare providers to make appropriate improvements. In addition to providing such evidence, the process of conducting clinical research also has a direct, protocol related, impact on the conduct of care of those individuals who consent to join clinical trials. Furthermore, this process may have a less direct but valuable effect on those healthcare institutions and services providing their care in trials as well as in daily practice through the impact of research activities upon staff, facilities and the culture of the institutions. Keeping the research agenda as a high priority for healthcare institutions enables maintaining intellectual curiosity, positive questioning of practices and search for optimal services to patients.

The conduct and outcomes of clinical research must translate into improved clinical care to justify the major investments it requires. Investigators interested in Translational Research recognise the important gap between laboratory and clinical research, which is sometimes termed the “first translational gap”. However, less attention has been paid to the gap between clinical research and the implementation of results to improve outcomes for patients across diverse healthcare systems and different populations – the “second translational research gap”. The usual approach to bridge the second translational gap is to disseminate positive trial results and explore their relevance to the widest possible patient population. However, the process of conducting clinical research within a healthcare system may be another way of bringing benefits to patients through research activity. Surprisingly, the benefits of research-active or research-intensive healthcare systems are poorly understood. The literature on the relationship between the process of clinical research and healthcare outcomes is sometimes confusing, and the main focus so far has been on therapeutic clinical research conducted in resource-rich healthcare systems.

The literature is marked by a lack of clarity on the key questions. A common question is whether patients treated within trials do better than similar patients treated in the same institution or healthcare service but outside trials. This effect is commonly referred to as a “participation effect”. Such comparisons are inherently biased by the selection criteria. Even attempts to produce comparable non-randomised control groups and to correct imbalances by multivariate analysis are largely unconvincing. Any benefits resulting from this participation effect can only likely to influence the outcomes of the minority of patients who actually participate in the trials.

A question of importance for many patients, healthcare professionals, and policy makers is “Do healthcare institutions or networks of service providers who are actively involved in clinical research tend to deliver better care and outcomes than those who are not?” The answer to this question is considered crucial by health professionals and researchers in order to determine whether conducting research (especially clinical and translational research) benefits patients and healthcare systems within which it is undertaken (Allen, 2010; EUROCAN, 2008). To answer this question, studies have to carefully define “research active” and ensure that all relevant patients in the compared institutions are included. Multivariate analysis is essential to determine whether the effect of research activity is independent and to address the level of causality between intervention and outcome. Such studies are uncommon because of their limited opportunities, the logistic difficulty of access to high quality and detailed data on both service outcomes and research activities in those services, and methodological complexity. As Allen (2010) elegantly observes “We must avoid the temptation to measure what we can count rather than measure what counts”. However, if it can be shown that in retrospect research activity is causally linked to improved outcomes, then prospectively this would provide added justification for the creation and funding of research activities and infrastructure, and then the benefits should be felt by all patients cared for in the research-active institutions and healthcare systems.

In September 2009 a workshop was held at the International Agency for Research on Cancer in Lyon, France. This workshop focused on the available evidence and the role of future research for a better understanding of the relationship between clinical research and healthcare outcomes. Particular interest was paid to the benefits of establishing research-intensive healthcare systems in the developed and developing world. The participants (shown below\*) were drawn from oncology, HIV research, methodological research and practice, and the world of healthcare policy development, both in developed and developing countries. The participants were interested in the benefits that may arise directly and indirectly from clinical research and bridging the second translational research gap.

The participants of the Workshop drew the following conclusions:

- Clarity about the question asked was vital for the progress in this field. Up to date, the literature has lacked clarity. The workshop participants concluded that the question about the benefits of developing research activity within a healthcare system was of considerable importance. Benefits from a research-intensive healthcare system should affect all patients cared for within that system, not only those actually included in research protocols. This question is particularly worthy of extensive further study, and the methodological challenges were outlined in the workshop. For understanding how increasing research activity may lead to improved healthcare outcomes, workshop participants suggested the theoretical framework of the Donabedian quality of care triad of structure-process-outcome (Donabedian, 1980).
- Substantial literature is available evaluating benefits for individual patients included in clinical research protocols compared to similar patients cared for in the same institutions. This “participation effect” has been quite extensively studied. Several reviews have been published (Braunholtz et al, 2001; Peppercorn et al, 2004; Vist et al, 2008). Overall, the workshop participants felt that this field was marked by methodological difficulties and stated a lack of convincing evidence that individual patients benefited from participation in clinical trials unless they were fortunate enough to benefit from being included in a test arm of a trial that proved to be significantly better than standard care.
- The literature is less extensive on the impact of research activity on the quality of healthcare outcomes within research-active institutions and healthcare systems in general. Only a few papers (du Bois et al, 2005; Karjalainen et al 1989; Majumdar et al 2008) including two articles published since 2000 have met the rigorous methodological standards (Figure 1 (a-d) and Figure 2 (a-b)). These reports provided evidence for benefits from the process of clinical research and improvement in healthcare outcomes. The workshop participants were encouraged that institutional research participation may improve the quality of healthcare probably by introducing state-of-the-art activities and technology, motivating clinicians, adherence to guidelines and providing a focus for workforce excellence. On the other hand, the data mainly relate to studies of treatments (not screening or prevention) and are hence limited; thus, no generalisations may be made with regard to resource-poor healthcare systems. In addition, bias resulting from selection, treatment and participation effects may effect the results reported from the literature.
- Some preliminary evidence was provided (Sullivan, unpublished) that a research active system per se (ie clinicians engaged in ANY sort of research) seems to improve clinical performance.
- Research activity, whether in screening or therapy, significantly changes the process of care. Studies on screening for cervical cancer in the developing world were discussed. Not only have these shown the feasibility and effectiveness of screening in several low income countries but also through the introduction of new technologies, staff training and the

development of clinical care teams, there is reason to expect that there would be improvements in healthcare outcomes that would go beyond the trial.

- The workshop summarised the efforts made across the world, particularly in the United Kingdom and the rest of Europe, to develop a comprehensive infrastructure within healthcare systems to support and promote clinical research. The effectiveness of these approaches in developing more intense healthcare systems was presented in the workshop. However, approaches vary between countries and depend critically on the nature of the healthcare system and the nature of the clinical academic research systems. In some countries, infrastructure has been focused on healthcare, as in the National Health Service in the UK, and in others around Clinical Trials Units and academic institutions.
- There is a pressing need for more research in this area, and workshop participants identified at least three research types:
  - Large, rigorous quantitative studies in which outcomes in research active healthcare systems are compared to similar healthcare systems which are research-inactive or less active. Such studies are not only methodologically demanding, but also potentially expensive and logistically difficult. The workshop participants felt that opportunities should be sought to link evaluations of research benefits with large regional or national service quality evaluations to make such studies feasible and affordable. Measures of research activity will be mainly numbers of studies and people recruited but may also include bibliometric studies.
  - Descriptive studies evaluating the impact on whole healthcare systems of clinical research initiatives are valuable and may be particularly important for obtaining information about the benefits of research in the developing world as comparative whole healthcare outcome data sets will be rare in these countries.
  - If a causal link between research intensive healthcare systems and improved outcomes is demonstrated, it becomes important to understand the mechanisms involved in order to allow us to maximise the benefits and to take account of these in designing clinical research.

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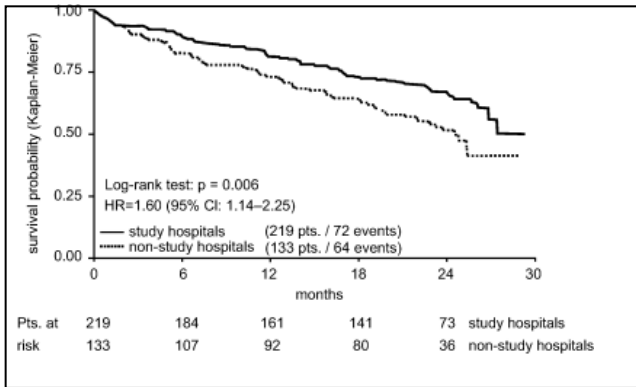
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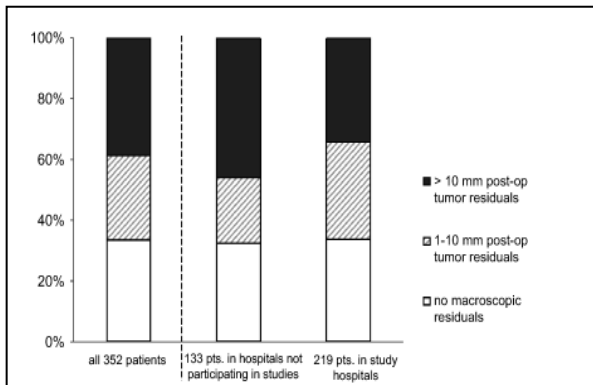
**Figure 1a: Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer**

*Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer. Du Bois et al, Int J Gynecol Cancer 2005, 15, 183.*

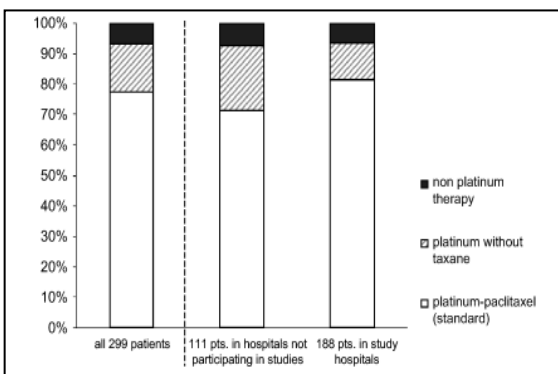
Du Bois et al (Figure 1a) took advantage of a Germany-wide audit of all outcomes in epithelial ovarian cancer to collect comprehensive unselected data from all institutions providing such care. They defined being research active as any accrual into the national collaborative group trials and showed that research active hospitals had consistently better outcomes for *all of their patients* than those that were not research active (highly significant on multivariate analysis) (Figure 1b). Hospital size was not a predictor of better outcomes. They also had systematically better adherence to guidelines with provision of state-of-the-art quality of care in surgery and chemotherapy (Figures 1c and 1d).

Variable	Hazard ratio	95% Confidence interval	P value
Stage	1		
	4.01	2.11-7.62	<0.0001
PS	1		
	3.00	2.03-4.44	<0.0001
Ascites	1		
	1.91	1.35-2.71	0.0002
Institutional study participation	1		
	1.82	1.27-2.61	0.001
Comorbidity	1		
	1.77	1.23-2.54	0.002
Age	1		
	1.76	1.18-2.64	0.006
Histology, Grading and Hospital Volume were NS			

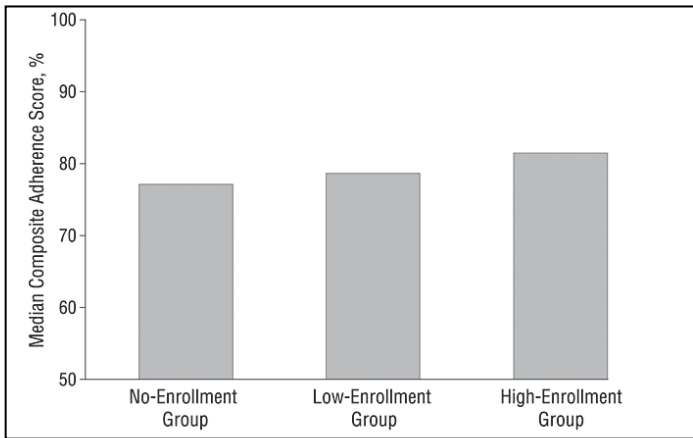
**Figure 1b: Prognostic factors for survival in invasive epithelial ovarian cancer in Germany 2001**



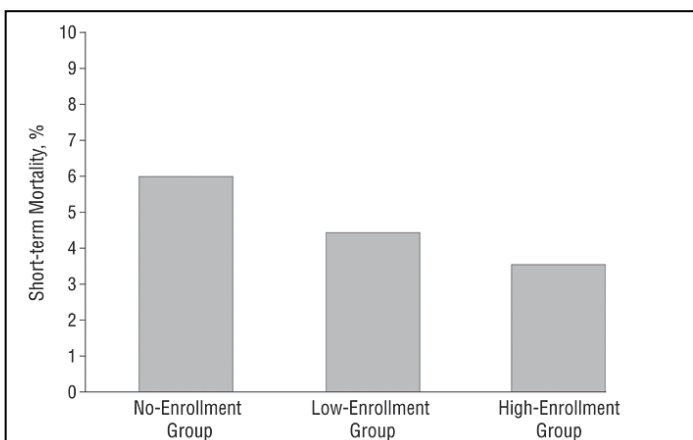
**Figure 1c: Post-operative residual tumour**



**Figure 1d: Selection of chemotherapy**



**Figure 2a: Better outcomes for patients treated at hospitals that participate in clinical trials: adherence**



**Figure 2b: Better outcomes for patients treated at hospitals that participate in clinical trials: mortality**

*Better outcomes for patients treated at hospitals that participate in clinical trials. Majumdar et al, Archives of Internal Medicine 2008, 168, 657.*

Majumdar et al evaluated all patients treated for coronary artery syndrome in US hospitals and defined tertiles of trial participation as none (145 hospitals), low enrolment (226 hospitals) and high enrolment (123 hospitals). Among 174,006 patients with coronary artery syndrome there were improvements in research active hospitals in the process of care shown by adherence to guidelines (Figure 2a) and in outcomes shown by short term mortality (Figure 2b) which remain highly significant on multivariate analysis.